CuraGen Corporation

Technologies to Design Protein-Specific Drugs

The pharmaceutical industry must keep a constant flow of new drugs through the research and development pipelines and onto the market in order to provide innovative medications to treat disease. Due to the difficulties in identifying appropriate gene protein targets, as well as high preclinical failure rates, industry estimates showed that only one-third of the new drugs needed in the fight against cancer, heart disease, and other complex disorders would be introduced. In 1994, CuraGen Corporation and American Cyanamid formed a joint venture to identify the affected genes for these diseases to provide a less expensive and shorter process to identify potential targets for new types of drugs. In addition, the companies sought to develop a companion technology to screen these drugs against disease targets using knowledge of the genome.

CuraGen and American Cyanamid requested Advanced Technology Program (ATP) support to combine state-of-the-art methods in molecular biology, structural biology, statistical mechanics, and computation methods to screen genes efficiently. The technical risk was high, because the project required discovering appropriate protein targets related to a specific disease, determining the genetic pathway of the disease that expresses the protein, and discovering effective new drugs. ATP awarded cost-shared funding for a three-year project that began in 1995.

American Cyanamid was acquired by American Home Products Corp. (AHP) in 1995, just before the project began. CuraGen and AHP (later renamed Wyeth Pharmaceuticals) used the funding to develop a wide array of analysis technologies to help the pharmaceutical industry identify biological pathways that play a role in disease and new drug candidates. The key technical advance was the capability of a high-throughput operation to identify genes whose protein products interact with each other.

CuraGen disseminated these technologies through research collaborations, database subscriptions, and internal development programs. CuraGen received 15 patents for protein–protein interactions discovered by PathCalling, Curagen's proprietary software. CuraGen was restructured in 2003 and 2004 when a "service model" to the pharmaceutical industry was no longer considered viable. As of 2005, CuraGen primarily used ATP-funded technologies for internal programs to identify targets and drug candidates for its own drug discovery and development programs. This strategic move has allowed the company to create a therapeutic pipeline of drug candidates for cancer, inflammatory disease, and diabetes.

COMPOSITE PERFORMANCE SCORE
(based on a four star rating)
* * * *

Research and data for Status Report 94-01-0404 were collected during September – November 2004.

New Drug Screening Is Complex

By the early 1990s, the top two major uncured diseases, atherosclerosis (the principal cause of heart attack and stroke) and cancer, cost the U.S. economy more than $200 billion per year. These diseases were responsible for more than 50 percent of all mortality in the United States.

Biotechnology experts were developing new drugs to protect patients from multiple diseases, such as cancer and atherosclerosis, and to save lives. The new drugs target specific cells in the human body to increase or decrease certain protein functions. Proteins perform many of the tasks to keep the body alive, such as breaking down glucose for energy, building cell walls, constructing new proteins, allowing the cell to reproduce, breaking down waste, and fighting infection. Most human diseases involve protein abnormalities, and most drugs target proteins in an attempt to correct the abnormalities that cause disease (for example, overproduction, underproduction, or a failure to function).

Cancer and atherosclerosis are both triggered by specific events that take place among the proteins that are associated with genes. The hierarchical, organized patterns of events are often referred to as genetic "pathways" or "cascades." Understanding these pathways at their fundamental, molecular level within the context of a disease is essential to developing a cure. There were no methods to screen protein libraries for interaction with potential drug targets. Nor was there any real method of understanding how the different molecular units, or amino acids, of each protein would individually react to target drug application.

The human genome contains about 60,000 genes. However, only certain subsets of these genes are suitable drug targets. The two main bottlenecks in drug discovery and development are identifying which protein targets may respond to drugs and which targets are relevant in disease.

Two companies, CuraGen Corporation and American Cyanamid, created a joint venture and proposed to identify methods that would enhance the total throughput of drug screening.

Protein Analysis Technology Holds Promise with Risk

CuraGen and American Cyanamid applied for cost-shared funding from ATP in 1994 because adequate internal and third-party funds were not available at the time for this type of high-risk research. It would be difficult to find appropriate protein targets, determine the genetic pathways, integrate multiple types of data (for example, pathway information and gene expression levels), and find effective new therapeutic compounds. Furthermore, a key constraint was to develop a screening technology suitable for a genomic approach. This means that the assay or test would have to be applicable to virtually every amino acid sequence composing a protein domain (just as DNA analysis technology is applicable to virtually every nucleic acid sequence).

The two main bottlenecks in drug discovery and development are identifying which protein targets may respond to drugs and which targets are relevant in disease.

CuraGen, founded in 1991, was an emerging biotechnology firm located in Branford, Connecticut. The company's mission was to systematically catalog disease-related proteins and to develop the tools needed to rapidly produce chemical compounds specific to these targets. American Cyanamid was acquired by American Home Products Corp. (AHP) in 1995. AHP (later renamed Wyeth Pharmaceuticals) was a publicly held, Fortune 100, chemical and life sciences company that discovered and developed medical and agricultural products and manufactured and marketed these products throughout the world. Of AHP's five major medical research efforts, its most important work related to oncology and cardiovascular disease.

ATP agreed to provide cost-shared funding for the project, which began in 1995.

Traditional functional genomic methods screened a single protein target for interaction against a library of proteins. CuraGen intended to develop tools to screen multiple proteins simultaneously. CuraGen's approach had two tiers. The first was to identify short protein segments (protein building blocks known as amino acids), called peptides, connected with the problematic protein–protein interactions related to disease. They would create enormous combinatorial libraries of peptides by mixing and matching the 20 kinds of amino acids, and they would then identify those peptides in the libraries that bind to the disease-related proteins. The second tier was to develop unique computational and structural analysis techniques to determine the salient chemical and physical features of the selected peptides

that enable them to block the disease-related proteins. The principles learned from that exercise would serve as technical guidelines for designing future therapeutic drugs carrying the same biomedical functions.

The approach directly applied to understanding and diagnosing multiple disease processes including genetic disorders, cancer, and viral infections. To pursue the development of their "molecular recognition technology," CuraGen assembled a staff with expertise in molecular biology, spectroscopy, statistical mechanics, nanofabrication, and computational methods. AHP provided medicinal chemists and structural biologists to develop three-dimensional search techniques for small molecules, called organic mapping.

CuraGen intended to develop tools to screen multiple proteins simultaneously.

The structural biology and organic-mapping tools that CuraGen hoped to create with ATP's help were enabling technologies. These tools could stimulate substantial industrial investigation in these high-risk areas, and success would have a significant impact on the process by which therapeutics are discovered.

CuraGen intended to develop new drugs to treat major diseases by identifying molecules that block abnormal protein–protein interactions. As a direct consequence of the speed and high-resolution three-dimensional structural information provided by the molecular recognition technology, the costs of developing such drugs were expected to be lower, and the time to clinical trials would be reduced. Moreover, the use of molecular recognition technology, together with other state-of-the-art technologies, had the potential to result in the discovery of breakthrough drugs for treating uncured diseases. The impact of these uncured diseases on the economy vastly exceeded the aggregate annual revenues of the pharmaceutical/biotechnology industry.

Molecular recognition technology was expected to accomplish the following:

- Reduce the time and cost of identifying novel, small organic molecules (new drugs) that bind to disease-related target proteins as well as the interactions between drugs and proteins
- Reduce preclinical experimental failures resulting from the application of unrefined drug design tools by focusing on protein–protein interactions
- Reduce failure rates through an understanding of molecular recognition, and, as a result, (1) enable better choices of target protein modules for which therapeutics can be designed and (2) ensure greater target module specificity (reduced side-effects)

AHP estimated that CuraGen's process would reduce lead development from two years to six months. The process had the potential to reduce costs by 88 percent. CuraGen hoped to develop a process that would reduce drug development time by approximately 60 percent and reduce the cost of development by approximately 70 percent. If successful, this would result in a savings of $1.5 million in preclinical costs for every successful drug. Cost and time savings could benefit millions of cancer and heart disease patients awaiting new drug therapies.

The ATP-funded project addressed four primary focus areas:

- **Molecular biology.** The CuraGen team needed to construct a library of proteins, understand how to recognize biochemical targets, select biochemical controls, and analyze target interactions.
- **Experimental structure.** CuraGen intended to synthesize peptides and measure distances between atoms within a molecule.
- **Computational modeling.** The team would develop experimental constraints and predict relevant molecule conformations (arrangements of molecules in space). They would confirm protein–protein interactions by genetic testing.
- **Organic mapping.** AHP would develop three-dimensional search programs to select molecules from a database with similar arrangements of atoms.

CuraGen would confirm results by analyzing the structural basis for biological functions of proteins coded by a specific gene, genetically testing protein–protein interactions, and by conducting *in vitro* and *in vivo* tests. Yale University performed experiments using radioisotopes to measure the efficiency of in vitro translations.

Protein Analysis Results Exceed Expectations

CuraGen studied interactions between pairs of proteins that have been linked to cancer in humans (RAS and RAF, vEGF and KDR). Researchers introduced the genes encoding those proteins into bacteria and yeast cells as a means for reproducing the proteins. They tested the proteins produced by the modified cells against their diversity library, looking for substances that interrupt interactions between the pairs of proteins.

CuraGen collaborated with Pennsylvania State University to measure distances between nuclei. They developed a method to simultaneously measure multiple distances in a single experiment. The purpose was to pick out the active form of a peptide, search for similar molecules in the database, and design new molecules.

The final focus areas were called Multiplexed Interaction Method (MIM), protein inhibitor screening, molecular structure, and organic mapping. MIM, which derived from the molecular biology focus area, screened protein–protein interactions and observed metabolic pathways in order to determine disease-specific targets for drug screens (see Figure 1).

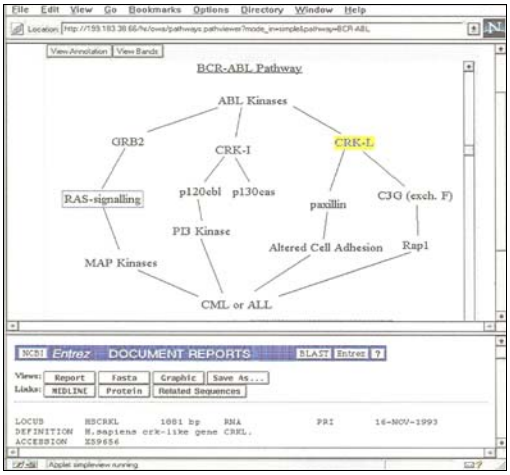

Figure 1. CuraGen's proprietary bioinformatic software allowed researchers to view protein pathways and access genomic databases to recognize additional functional and biochemical information about the proteins interacting in the pathways.

AHP generated two new genetic databases for data mining, as well as algorithms to search for pharmacophore similarities (three-dimensional substructure of a molecule that carries the essential features responsible for a drug's biological activity).

Cost and time savings could benefit millions of cancer and heart disease patients awaiting new drug therapies.

CuraGen also developed a tool, the CombiGen system, to efficiently identify small-molecule drugs that can potentially bind to protein targets or block disease-related protein–protein interactions. The key advance of this system is that it can screen thousands of targets simultaneously.

The project's structure analysis led to developing a bioinformatics software, called PathCalling (see Figure 2), that extracts consensus information from MIM data. PathCalling identifies biological pathways that play a role in disease. The process starts with a set of genes that are associated with a disease. High-throughput biological methods search for other genes that are part of the same pathway. These genes are then re-introduced into the PathCalling system to extend the pathway. The key technical advance of PathCalling is the capability of the high-throughput operation to identify genes whose protein products interact with each other.

The second structural advance was another software tool, HitCalling, that screens the proteins associated with a particular gene identified by PathCalling against small-molecule diversity libraries. HitCalling identifies both binding and inhibition in protein–protein interactions with a potential drug. Small molecules identified in the screens are drug candidates that can be optimized using traditional technologies, then advanced into preclinical and clinical trials. HitCalling provides a uniform assay or sample format, without the need for individual assay development, for every drug-screening target. This allows all the proteins in a pathway to be screened and permits multiple targets to be screened simultaneously. As a result, researchers can screen more molecules faster compared with existing drug-screening technologies.

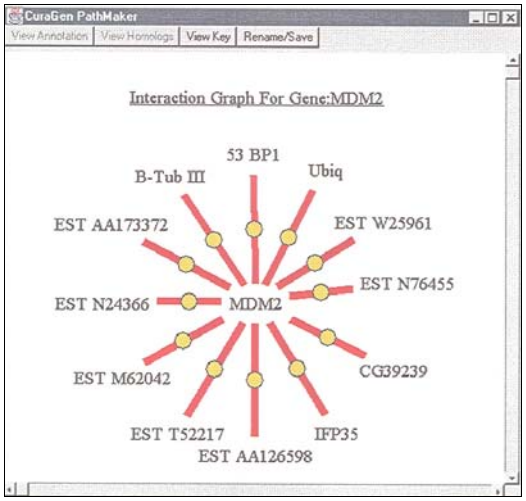

Figure 2. Sample screenshot from CuraGen's PathCalling (formerly called PathMaker) proprietary software. The sample shows the interaction graph for a gene, MDM2.

Building on techniques developed under the ATP-funded project, CuraGen collaborated with Yale University and received another award in 1996 from Connecticut Innovations, Inc. to pursue nuclear magnetic resonance (NMR) applications. (NMR spectroscopy provides information on the position of specific atoms within a molecule by using the magnetic properties of the cell nuclei.) The new work complemented the ongoing development of high-throughput methods for structural analysis of the ATP-funded project. They extended NMR methods from peptides to general organics, which offered greater diversity for drug screening.

AHP also developed a three-dimensional search algorithm to allow rapid mapping of biologically active peptides with similar pharmaceuticals. This development was completed and discontinued in 1997.

CuraGen Identifies Proprietary Protein–Protein Interactions

CuraGen successfully developed tools to screen multiple proteins simultaneously. The key performance criterion for the project was to reduce the rate of false positives, which is the incorrect identification of possible protein targets. Reducing the false-positive rate provides several benefits:

- The system sampled 10 to 100 proteins at a time, rather than 1 at a time (searching through a library of millions of other proteins for interactors).
- Entire libraries could be screened against each other to discover a large set of protein–protein interactions, each a potential drug-screening target.
- The cost of generating information would be greatly reduced. Much of the cost arises from sequencing the DNA of all the genes that express the protein to analyze the interacting proteins. Reducing the false-positive rate reduces the sequencing cost by a factor of 10.

The cumulative effect of these advances enables the molecular recognition technology to systematically identify new targets for drug screening. These are novel, pharmaceutically relevant genes and expressed proteins that are associated with specific diseases.

By the end of the ATP-funded project, the PathCalling database contained several thousand proprietary protein interactions, approximately five times more interactions than the closest industry competitor had compiled. Results from PathCalling indicated that it would be possible to use consensus information to identify the protein domain that participated in protein–protein interactions, which would aid in structure-based drug design against these targets.

The company's technology development has had the following additional benefits:

- The infrastructure for PathCalling provides a system for identifying proteins that are in the same pathway as known disease-related proteins.
- Many of the protein domains discovered through PathCalling are novel coding sequences.

CuraGen met or exceeded all of its technical goals for the ATP-funded project. The goals were to reduce the time and cost of identifying novel small organic molecules that bind to disease-related target proteins (new drugs), reduce experimental failures by focusing on protein–protein interactions, and increase understanding of molecular recognition in order to (1) better select target protein modules for which therapeutics can be designed and (2) ensure greater specificity (reduced side-effects). By project completion in 1998, CuraGen's propriety MIM, PathCalling, and

HitCalling technologies met or exceeded the technology project goals:

- Construct one genomic library per month (met goal)
- Construct 4,000 samples for testing against the libraries per month (exceeded goal of 48 per month)
- Prepare 20,000 templates per month (exceeded goal of 2,000 per month)
- Sequence 20,000 samples per month (exceeded goal of 2,000 per month)
- Confirm 1,000 protein–protein interactions per month (exceeded goal of 100 per month)
- Discover 200 new interactions per month (exceeded goal of 50 per month)

CuraGen is using MIM, PathCalling, and HitCalling in several modes:

- Screening genome versus genome for simple organisms, such as microbial pathogens. These types of screens were previously impractical because true interactions would be overwhelmed by a background of false positives.
- Screening tens to hundreds of protein domains versus protein libraries in order to identify protein–protein interactions relevant to human disease. The improved technology for preparing the protein domains and libraries has allowed the implementation of a systematic workflow to generate and capture information.
- Completely screening interactions between proteins in the yeast genome (initiated in collaboration with Dr. Stanley Fields, inventor of the yeast two-hybrid system). Interactions discovered in yeast often mirror interactions between homologous proteins in humans. A database of the complete set of yeast interactions could therefore be a valuable asset for drug discovery.
- Patenting protein–protein interactions for use as targets in drug screening.

The CuraGen relied on a combination of hypothesis-driven disease models, drug-response models, gene- and pathway-mining approaches, and human genetics. The company is developing a broad pipeline of protein, antibody, and small-molecule drugs in the areas of oncology, inflammatory diseases, obesity, and diabetes.

With HitCalling, CuraGen developed a high-throughput protein analysis tool that can accept targets directly from upstream genomics processes such as PathCalling. This removes the bottleneck in creating a new assay or sample for each target. Furthermore, the number of targets entered into screens can keep pace with the number of targets discovered through genomics. In addition to screening targets identified through PathCalling, the HitCalling assay system can also be used to screen other targets.

CuraGen is developing a broad pipeline of protein, antibody, and small-molecule drugs in the areas of oncology, inflammatory diseases, obesity, and diabetes.

After the ATP-funded project, CuraGen initiated a collaboration with the Massachusetts Institute of Technology to continue developing HitCalling technology. CuraGen has also sought collaborations with academic groups engaging in combinatorial synthesis as a source of drug-screening libraries.

Molecular Recognition Technologies Yield New Drug Screening

CuraGen sold subscriptions to the PathCalling database to Genentech and Biogen. CuraGen obtained numerous patents for protein–protein interactions discovered by PathCalling. The patents cover more than 90 protein-protein interactions as targets in identifying potential drugs. Moreover, the company obtained additional drug-screening libraries from ArQule, a leader in combinatorial chemistry, to further utilize CuraGen's protein-screening technologies.

CuraGen has shared these technologies through research collaborations, database subscriptions, and internal programs. In one research collaboration, CuraGen analyzes disease-related genes and applies

its MIM research services in conjunction with PathCalling to reveal additional proteins in the same pathway. CuraGen then uses HitCalling to identify drug candidates. Database subscriptions permit subscribers to search through the company's database of biological pathways to identify proteins that could be licensed for use in drug discovery assays. CuraGen has established research collaborations and, for a time, provided database subscriptions that provided access to PathCalling. As of 2005, CuraGen was using PathCalling and HitCalling in internal programs to identify targets and drug candidates for its own drug discovery and development programs.

Other dissemination efforts include delivering information over the Internet to collaborators. GeneScape is CuraGen's web-based bioinformatics system that incorporates real-time process management, data analysis, and data visualization. GeneScape provides access to CuraGen's complete technology platform, including GeneCalling (developed under a separate ATP award) to discover disease-related genes and CuraTools for web-distributed bioinformatics. CuraGen is currently collaborating with leading life science companies Genentech, Biogen, and Pioneer Hi-Bred International.

Technical Success Leads to Drug Pipeline

CuraGen announced its initial public offering in 1998 for $34.5 million. Without ATP funding, CuraGen would not have had the resources to pursue PathCalling in parallel with other programs. According to company representatives, the development of PathCalling and HitCalling would have been delayed by at least two years. CuraGen worked with ATP on this project, as well as on two others (94-05-0027, Integrated Microfabricated DNA Analysis Device for Diagnosis of Complex Genetic Disorders; 96-01-0141, Programmable Nanoscale Engines for Molecular Separation), so ATP has played an integral role in the development of CuraGen's potential commercial drug offerings.

Since its inception, CuraGen's stated strategy has been to discover new ways to treat disease by understanding how the expressed proteins from genes function within the human genome. With the help of ATP, the company has identified disease-related genes and their therapeutic targets that has led to the development of unique pharmaceutical products.

CuraGen was restructured beginning in late 2002, because the business strategy of supplying tools and services to the pharmaceutical industry was no longer viable. Profit margins were too thin, and financing was shifting to companies pursuing proprietary pharmaceuticals.[1,2] According to Johnathan M. Rothberg, CEO, "CuraGen competed successfully in the race to discover drug targets from the human genome and…has emerged with a wealth of knowledge about the molecular basis of disease…We must now focus our resources with greater intensity on drug-development projects that are designed to turn these targets, and this knowledge of disease, into cures for unmet medical needs."[3]

As a result of CuraGen's accomplishments, the company has collaborated with numerous companies, including Abgenix, Biogen, Genentech, Seattle Genetics, and Bayer, and now has an extensive pipeline of protein, antibody, and small therapeutics to treat cancer, inflammatory disease, and diabetes. The company's most advanced projects are in clinical development.

In December 2004, CuraGen received its first "fast track" designation from the U.S. Food and Drug Administration for a novel protein therapeutic being developed for the treatment of oral mucositis (a complication of chemotherapy, which leads to painful ulceration of the mouth and throat). CuraGen is collaborating with a biopharmaceutical company, TopoTarget A/S, to develop a second small-molecule drug, a histone deacetylase (HDAC) inhibitor. HDAC inhibitors appear to restore a normal balance in the expression of genes in cancer cells, making them susceptible to radio and chemotherapy to directly treat solid and hematological cancers. This drug is currently in a Phase II clinical trial for the treatment of multiple myeloma. Two additional clinical development programs are ongoing in 2006: a

[1] Mullin, Rick. "Drug Discovery: Pure Science Yields to Applied Science as the Genomics Revolution Focuses its Energy on Commercialization." *Chemical & Engineering News*, Vol. 81, No. 30. pp. 21-31, July 28, 2003. http://pubs.acs.org/cen/coverstory/8130/8130drugdiscovery.html

[2] Higgins, Steve. "New Haven, Conn., Biotechnology Firm Cuts 110." *Knight-Ridder Tribune Business News*, No. 4390393, October 20, 2004.

[3] "Focusing on Drug Development (Restructuring)." *R&D Directions*, Vol. 9, No. 1, January 2003.

third antibody has completed Phase I testing for kidney inflammation; and a fourth antibody drug candidate is beginning clinical trials for metastatic melanoma. CuraGen is also using the ATP-funded technology to select promising candidates from TopoTarget's extensive library of HDAC inhibitors for clinical development.

Conclusion

In this joint venture, CuraGen and American Home Products Corp. (later renamed Wyeth Pharmaceuticals) used molecular biology methods, structural physics, and computational statistical mechanics to determine how proteins interact and to identify structures likely to bind to (and thus block) disease-related proteins. The project began in 1995. The CuraGen joint venture accomplished the following: 1) reduced the time and cost of identifying novel small organic molecules (new drugs) that bind to disease-related target proteins; 2) reduced preclinical experimental failures resulting from the application of unrefined drug design tools by focusing on protein–protein interactions; and 3) reduced failure rates through an improved understanding of molecular recognition. CuraGen's success resulted in finding better choices of target protein modules for which therapeutics can be designed and greater target module specificity (reduced side-effects). CuraGen's proprietary process, Multiplexed Interaction Method, screens protein–protein interactions and determines their metabolic pathways. The company's PathCalling software tests simultaneously for interactions between billions of combinations of proteins and assembles them into a database of biological pathways of genes whose protein products interact. HitCalling software, also resulting from this research, screens the identified genes against libraries of molecules that might be candidate drugs.

CuraGen was awarded 15 patents for these advances and published its findings in academic journals. The U.S. Food and Drug Administration awarded one CuraGen drug candidate "fast track" designation for treating oral mucositis. As of 2005, the company had developed a pipeline of drug candidates to treat cancer, inflammatory disease, and diabetes.

PROJECT HIGHLIGHTS
CuraGen Corporation

Project Title: Technologies to Design Protein-Specific Drugs (Molecular Recognition Technology for Precise Design of Protein-Specific Drugs)

Project: To design drugs with a strategy in which short protein segments that bind to disease-related proteins serve as leads for non-protein therapeutic agents aimed at major illnesses, including cancer and cardiovascular disease.

Duration: 3/1/1995 - 2/28/1998
ATP Number: 94-01-0404

Funding (in thousands):

ATP Final Cost	$2,379	40.0%
Participant Final Cost	3,580	60.0%
Total	$5,959	

Accomplishments: With ATP funding, CuraGen Corporation and its joint venture partner, American Home Products Corp. (later renamed Wyeth Pharmaceuticals), accomplished the following:

- Developed a process, Multiplexed Interaction Mapping, to discover protein–protein interactions.
- Developed PathCalling software to test for interactions between billions of combinations of proteins and assemble them into a database of biological pathways of genes whose protein products interact. The software allows scientists to extract data from a given interacting pair of genes and view the proteins in text or graphical formats.
- Developed HitCalling software to screen the identified genes against libraries of molecules that might be candidates for drugs.
- Developed the CombiGen system to identify small-molecule drugs that can potentially bind to protein targets or block disease-related protein–protein interactions. The system can screen thousands of targets simultaneously.

CuraGen Corporation received the following 15 patents related to the ATP-funded technologies. The patents protect more than 90 protein–protein interactions as targets in identifying potential drugs.

- "Consensus configurational bias Monte Carlo method and system for pharmacophore structure determination"
  (No. 6,341,256: filed March 31, 1995, granted January 22, 2002)
- "Method for distance measurements with solid-state NMR"
  (No. 6,027,941: filed May 15, 1996, granted February 22, 2000)
- "Identification and comparison of protein–protein interactions that occur in populations"
  (No. 6,083,693: filed June 14, 1996, granted July 4, 2000)
- "Method of using solid state NMR to measure distances between nuclei in compounds attached to a surface"
  (No. 6,150,179: filed July 11, 1996, granted November 21, 2000)
- "Identification and comparison of protein–protein interactions that occur in populations and identification of inhibitors of these interactors"
  (No. 6,057,101: filed June 13, 1997, granted May 2, 2000)
- "53BP2 complexes"
  (No. 5,977,311: filed September 23, 1997, granted November 2, 1999)
- "CDK2 interactions"
  (No. 5,986,055: filed November 13, 1997, granted November 16, 1999)
- "NLK1 protein and NLK1 protein complexes"
  (No. 6,476,193: filed October 6, 1998, granted November 5, 2002)
- "Identification and comparison of protein–protein interactions that occur in populations and identification of inhibitors of these interactors"
  (No. 6,395,478: filed January 12, 1999, granted May 28, 2002)
- "Isolation and characterization of Hermansky Pudlak Syndrome (HPS) protein complexes and HPS protein-interacting proteins"
  (No. 6,573,364: filed March 10, 1999, granted June 3, 2003)
- "HsReq*1 and hsReq*2proteins and use thereof to detect CDK2"
  (No. 6,521,412: filed June 22, 1999, granted February 18, 2003)
- "53BP2 complexes"
  (No. 6,627,405: filed June 22, 1999, granted September 30, 2003)
- "Identification and comparison of protein--protein interactions that occur in populations and identification of inhibitors of these interactors"
  (No. 6,410,239: filed December 14, 1999, granted June 25, 2002)

PROJECT HIGHLIGHTS
CuraGen Corporation

- "Nucleic acid encoding the MDM interacting protein" (No. 6,372,490: filed February 22, 2000, granted April 16, 2002)
- "Protein–protein complexes and methods of using same" (No. 6,753,314: filed March 29, 2000, granted June 22, 2004)

Commercialization Status: CuraGen's commercialization model is multi-pronged. The first prong is internal, in which the company uses its PathCalling and HitCalling technologies primarily for in-house drug development. The second is subscriptions to its Pathcalling database, which subscribers can search to find proteins that can be licensed for use in drug discovery assays. Licensing will be the third prong. CuraGen has sold subscriptions to the PathCalling database to Genentech and Biogen and has established collaborations with numerous pharmaceutical companies, such as Bayer, Biogen, and Genentech. Drug candidates in CuraGen's pipeline include treatments for cancer, inflammatory disease, and diabetes.

Outlook: The outlook for CuraGen's ATP-funded technology is excellent. The company recently received its first Food and Drug Administration "fast track" designation for one of its protein drug targets to treat oral mucositis (a complication of chemotherapy, which leads to painful mouth and throat ulcers), developed as a result of the ATP-funded technology. A second small-molecule drug is in Phase II clinical trials for the treatment of multiple myeloma. A histone deacetylase (HDAC) inhibitor, this drug directly treats solid and hematological cancers. A third antibody has completed Phase I testing for kidney inflammation; a fourth antibody drug candidate is beginning clinical trials for metastatic melanoma in 2006.

Composite Performance Score: * * * *

Number of Employees: 25 employees at project start, 150 as of December 2004

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Phone: (845) 602-5579

Publications: CuraGen researchers shared their project knowledge through the six publications and seven presentations listed below.

- Mueller, K.T., T.P. Jarvie, D.J. Aurentz, and B.W. Roberts. "The REDOR Transform: Direct Calculation of Internuclear Couplings from Dipolar-Dephasing NMR Data," *Chem. Phys. Lett*., 242, pp. 535-542, 1995.
- Deem, M.W., and J.S. Bader. "A Configurational Bias Monte Carlo Method for Linear and Cyclic Peptides," *Molecular Physics*, Vol. 87, pp. 1245-1260, 1996.
- Jarvie, T.P., G.T. Went, and K.T. Meuller. "Simultaneous Distance Measurements in Peptides via Solid State NMR: Application to Drug-Like Molecules," *Journal of the American Chemistry Society (JACS)*, Vol. 118, pp. 5330-5331, 1996.
- Liang, X.L., J.S. Bader, and G.T. Went. "The Bio-Active Conformations of the arginine-Glycine Aspartate Recognition Sequence," *JACS*, Vol. 118, pp. 5330-5331, 1996.
- Wrighton, N.C., et al. "Small Peptides as Potent Mimetics of the Protein Hormone Erythropoietin," *Science*, Vol. 273, pp. 458-463, July 1996.
- Uetz, Giot, Cagney, Mansfield, Judson, Knight, Lockshon, Narayan, et al. "A Comprehensive Analysis of Protein–protein Interactions in Saccharomyces Cerevisae," *Nature*, Vol. 403, pp. 623-631, 2000.

Presentations:

- Jarvie, T.P., K.T. Mueller, D.J. Aurentz, and G.T. Went. "Time and Frequency Domain Analysis of Solid-State NMR Signals: Isotropic Alternatives to the Fourier Transform." 37th Experimental NMR Conference, Asilomar, CA, March 1996.

PROJECT HIGHLIGHTS
CuraGen Corporation

- Liang, X.L. “Structural Characterization of a Group of RGD Peptides,” American Chemical Society National Meeting, New Orleans, LA, March 1996.

- Bader, J.S. “Configurational Bias Monte Carlo Algorithms for Bioactive Molecules,” American Chemical Society National Meeting, New Orleans, LA, March 1996.

- Bader, J.S. “Improved Algorithms for Conformational Sampling of Polymers,” University of Massachusetts invited talk, Amherst, MA, April 1996.

- Bader, J.S. “Regrowth Algorithms for Biosimulations,” Computational Chemistry Gordon Research Conference, New Hampton, CT, July 1996.

- Jarvie, T.P. and K.T. Mueller. “Simultaneous, Multiple Distance Measurements with the REDOR Transform,” Eastern Analytical Symposium, Somerset, NJ, November 1996.

- Mehta, V.D., and T.P. Jarvie. “Accelerating Drug Discovery and Development.” IBC’s Fifth Annual International Symposium, Philadelphia, PA, April 1998.